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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/611,310	07/01/2003	Ryoichi Hashida	3462.1004-000	3981

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EXAMINER	
CHAPPELL, CHERIE M	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 08/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/611,310	HASHIDA ET AL.	
	Examiner	Art Unit	
	Cherie M. Chappell	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3, 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.0

RESPONSE TO AMENDMENT

1. Applicant's amendment filed 31 May 2005 is acknowledged. Claims 1-3 and 31 are pending and under examination. Non-elected claims 4-30 and 32-53 have been cancelled by Applicant without prejudice.

Claim Rejections/Objections Withdrawn

2. The objection to the specification is withdrawn in response to Applicant's amendments.

3. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. An English translation of the foreign priority document was received by the Office on June 17, 2004 with a verification of translation, attached.

4. Applicant's IDS submitted on 6/17/2004 and 11/22/2004 is acknowledged and has been fully considered. Applicant is requested to submit a clean copy of the PTO-1449 form so that is can be signed.

5. The rejection of claims 1-3 and 31 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps is withdrawn in response to Applicant's amendment to claim 1 and cancellation of claims 4-30 and 32-53.

Claim Rejections Maintained/New Ground of Rejection

6. The rejection of claims 1-3 and 31 under 35 U.S.C. 112, first paragraph, as lacking enablement for the method of testing an allergic disease is withdrawn in part in response to Applicant's amendment to claim 1 and cancellation of claims 4-30 and 32-53. Applicant is enabled for diagnosing atopic dermatitis by the recited methods, but not for all allergic diseases.

In response to Applicant's arguments, the recitation of a method of testing for any allergic disease is generic and has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re*

Hirao, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

Applicant's amendment of claim 1 to include "an increase in the expression level of the gene in the eosinophil cells of the test subject is indicative of an allergic disease" within the body of the claim fails to address the concern of enablement raised by the examiner as to the broad claim of "allergic diseases". The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate with these claims.

At the time the invention was conceived, TINUR and TR3 (as well as NOT, NAK1, Nur77, Nurr1, NGFI-B, and RNR-1) (see specification p. 12) were known to function as general coactivators of gene transcription rather than as participants in the induction of specific target genes, as is the case with classical steroid receptors (Mages *et al.*, *Mol Endocrinol.* 1994 Nov; 8(11):1583-91). This lack of gene-specific targeting necessitates undue experimentation on the part of the skilled artisan to determine whether these genes are involved in all allergic diseases. Applicant correctly states that allergic diseases are considered to be multifactorial diseases and that multifactorial diseases are caused by the interaction of many different genes, the expression of each of which is independently influenced by multiple environmental factors (specification at 1, lines 13-16). Applicants have shown an increase in gene expression levels of TINUR and TR3 genes in human eosinophils in atopic dermatitis.

Moreover, the Nur subfamily members are orphan nuclear receptors because no ligand has yet been identified for them. The existence of such a ligand remains elusive, considering that these transcription factors are constitutively active in numerous cell lines (Maira, *et al.*, Mol Cell Bio. 1999 Nov, p. 7549-7557, at 7549 column 1, second paragraph), even in the absence of serum or any other exogenous agent (Paulsen *et al.*, 1992. J Biol Chem. 267:16491-16496, at 16496, first column, last paragraph). Comparative tissue distribution studies for Nur family submembers (including Nur77 and NOR-1) show that these genes are fairly widely expressed, and are in fact, both constitutively expressed in various peripheral tissues and in some regions of the brain (Maira, *et al.*, Mol Cell Bio. 1999 Nov, p. 7549-7557, at 7549 column 1, second paragraph). Applicants have only shown expression in eosinophils of atopic dermatitis patients.

Although the specification outlines art-recognized procedures for producing and screening related Nur family genes in eosinophils in atopic dermatitis, this is not adequate guidance as to the nature of expression of these genes in other allergic diseases, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if Nur family ligands in allergic diseases other than atopic dermatitis were identified in the specification, they may not be sufficient, as the

ordinary artisan would immediately recognize that a ligand would need to induce promoter activation in order to activate gene transcription. Paulsen *et al.*, discusses the inherent difficulty in determining whether this family of orphan receptors has ligands or whether they even require a specific ligand for activity (at 16496, first column, last paragraph). Further, gene transcription is not an accurate predictor of protein production (Hayes et al., Electrophoresis 1998; 19(11): 1862-1871, at 1862, section 2.1 - reference previously provided by examiner). Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and screen same for activation of these two genes in all forms of allergic disease, the lack of direction/guidance presented in the specification regarding which structural features are required to promote activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of constitutive activation of these transcription factors in numerous cell lines, and the breadth of the claims which fail to recite any limitations of allergic disease, other than atopic dermatitis, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention for all allergic diseases.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working samples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

7. Applicant's additional arguments filed 31 May 2005, with respect to claims 1-3 and 31 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly

owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. Claims 1-3 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nakajima T, *et al.*, *Blood.* 15 August 2001, Vol. 98. No. 4, pp. 1127-1134. Nakajima *et al.*, teaches a method of testing gene expression levels in eosinophils, including gene expression levels in patients with atopic dermatitis (p. 1131, column 1, second sentence) utilizing a high density (approximately 12,000 transcripts) oligonucleotide expression probe array (GENECHIP Human Genome U95A, AFFYMETRIX). Additionally, Nakajima *et al.*, teaches gene expression analysis by rt-PCR in the confirmation of the oligonucleotide gene expression results. Nakajima *et al.*, does not teach increased expression levels of TR3 or TINUR.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to determine the expression levels of TR3 or TINUR in eosinophils because both the TR3 and TINUR genes were present on the AFFYMETRIX U95A chipset used by Nakajima *et al.* The skilled artisan would have only had to look at the data to determine whether the expression levels of TR3 and TINUR were increased or decreased over controls in atopic dermatitis.

The person of ordinary skill in the art would have been motivated to make those modifications because the AFFYMETRIX U95A chipset already contained oligonucleotides for the TINUR gene (S77154 - NGFI-B/nur77 beta-type transcription factor homolog [human, T lymphoid cell line, PEER, mRNA, 2469 nt] and the HUMTR3A gene [L13740 – human TR3 orphan receptor mRNA, complete

cds]. Additionally, the person of ordinary skill in the art would have reasonably expected success because the data would have been readily available by anyone using AFFYMETRIX U95A chipset on eosinophils.

As a result of these new grounds for rejection, this action is made NON-FINAL.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cherie M. Chappell whose telephone number is (571) 272-3329. The examiner can normally be reached on Monday - Thursday 8:30am-7:00pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elizabeth C. Kemmerer

CMC

ELIZABETH KEMMERER
PRIMARY EXAMINER